Remarks

Status of Claims

Claims 80, 81 and 90-97 are pending in this application (of which claim 91 is currently withdrawn). No amendments are made herewith. Consideration and allowance of the pending claims is requested.

Response to Advisory Action

In the Final Office action dated June 10, 2010, the Office rejected claims 80, 81, 90 and 92-97 under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement. The Office asserted that the specification "lacks adequate guidance, direction or discussion to apprise the skilled artisan how the claimed compound may be used to achieve (1) the inhibition of GRP activity and (2) the disclosed utilities for treating conditions wherein GRP inhibition has been implicated" (Office action, at page 3). In response, Applicants submitted an Amendment and Response After Final Office Action on August 10, 2010 (hereafter, the "August Response").

The Office responded to the August Response with an Advisory Action dated August 26, 2010. Applicants thank the Office for entering to the record both the amendments and arguments submitted with the August Response.

In the Advisory Action, the Office has maintained the enablement rejection of claims 80, 81, 90 and 92-97 under 35 U.S.C. §112, first paragraph. Applicants traverse the maintained enablement rejection for the reasons of record and as discussed below. Applicants understand from the Advisory Action that the rejection of the current claims has been maintained in part because the Office will not consider scientific arguments made by Counsel. Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by Dr. Frank Cuttitta, an inventor listed in the application, in support of Applicants' position that one of skill in the art would be able to practice the claimed invention without undue experimentation,. In his Declaration, Dr. Cuttitta discusses GRP function, the support in the specification that the claimed compound is a GRP inhibitor, and his conclusions about the therapeutic applications of the claimed compound.

The claimed compound of formula XV' is compound 77427

The current claims are limited to methods of using "a compound of formula XV'." As Dr. Cuttitta states in the Declaration: "In the specification, and in the related published literature, this compound is also designated compound 77427. Thus, compound 77427 is synonymous with a compound of formula XV'" (Declaration, ¶7). For the sake of conformity with the nomenclature used in the description of the data provided in Applicants' specification (as well as the published literature), the claimed compound is referred to herein as compound 77427 (as it was also referred to in the August Response).

GRP affects cellular activity through stimulation of second messenger release

Applicants have previously described the varying biological processes affected by GRP (for further discussion of this, *see* the Amendment and Response to Non-Final Office Action, submitted on May 24, 2010). Dr. Cuttitta notes that GRP affects cellular activity through stimulation of cellular second messenger pathways (Declaration, ¶5). Additionally, Dr. Cuttitta notes that an inhibitor of GRP activity (*i.e.* a "pure antagonist") will not affect second messenger release in the absence of GRP:

> "GRP affects cellular function by stimulating the release of the second messenger IP_3 in cells expressing the GRP receptor. In cultured cells, in the absence of exogenously added or endogenously secreted GRP, a GRP-specific pure antagonist will have no effect on GRP-stimulated IP_3 release. GRP-stimulated activity is well known in the art to be associated with many biological processes, including cell proliferation, lung development, food intake, and control of blood pressure (Cuttitta *et al., Nature*, 316:823-826, 1985; Sunday *et al., J Clin Invest,* 102:584-594, 1998; Merali *et al., Neuropeptides*, 33:376-386, 1999; and Ohki-Hamazaki *et al., Nature*, 390:165-169, 1997; each of which is of record in this file)" (Declaration, ¶5).

Compound 77427 is an inhibitor of GRP function

In the August Response, Applicants argued that one of skill in the art would understand from the specification that compound 77427 is an inhibitor of GRP function (August Response, at pages 5-6). Applicants supported this argument by pointing to those portions of the specification and subsequently published papers that detail the identification and characterization of compound 77427 as an inhibitor of GRP function. This has now been reiterated in greater

detail by Dr. Cuttitta in his Declaration. Dr. Cuttitta describes the identification of compound 77427 as a GRP inhibitor as follows:

> "Compound 77427 was identified as a GRP inhibitor by primary and secondary screens of a small molecule library. The primary screen identified compounds that blocked the interaction between GRP and a GRP-binding antibody that inhibits GRP function (*i.e.* a neutralizing antibody). This screen is set forth schematically in Figure 1A of the specification. The secondary screen tested the ability of the compounds identified in the primary screen to **affect GRP activity in cultured cells expressing the GRP receptor** (*i.e.* test the ability of the compounds that were identified to block the binding of the GRP-binding antibody to stimulate or inhibit GRP activity). Non-small cell lung carcinoma H1299 cells were used in the secondary screen; H1299 cells are known in the art to express the GRP receptor (*see* Moody *et al.*, *J. Cell. Biochem. Supp.*, 24:247-256, 1996; provided herewith as **Exhibit B**), but these cells do not express significant amounts of GRP (*see* Giaccone, *J. Cancer Res. (Supp.)*, 52:2732s-2736s, 1992; provided herewith as **Exhibit C**). Figure 3 of the specification presents data from the secondary screen. Figure 3A shows that in the absence of any additional GRP or compound (control), relatively little IP_3 release is detectable. This confirms that the H1299 cells secrete little if any GRP into the culture media, and also determines the baseline of IP_3 release (non-GRP stimulated) in the cell cultures. When GRP is added to the culture media, the level of IP_3 released is significantly increased. This confirms that the H1299 cells express the GRP receptor, and that exogenously-added GRP will stimulate IP_3 release. In contrast, when both GRP and compound 77427 are added to the culture media, relatively little IP_3 is released" (Declaration, ¶8).

Based on the results of the primary and secondary screens described above, Dr. Cuttitta concludes that "compound 77427 inhibits the IP_3-stimulating activity of GRP. Moreover, because GRP function is dependent on the ability to stimulate second messenger release, I conclude that these results also indicate that compound 77427 will inhibit all known GRP activities. This conclusion is further supported by additional data provided in the specification" (Declaration, ¶9)." As discussed in detail below, this additional data is presented in Figures 5 and 6 of the specification.

Compound 77427 inhibits GRP activity in vitro *and* in vivo

As discussed in the August Response, Figure 5 of the specification shows the effect of compound 77427 on GRP-stimulated angiogenesis *in vitro*. Dr. Cuttitta describes the data shown in Figure 5 as follows:

"Figure 5 shows the effect of GRP and compound 77427 on *in vitro* endothelial cell preangiogenic cord formation. In the absence of GRP, relatively few endothelial cell cord structures are formed (top). When GRP is added, abundant endothelial cord structures are observable (middle). When GRP is added together with compound 77427, relatively few cord structures are observed (bottom). Thus, compound 77427 inhibits GRP-stimulated cord formation activity. This and similar results have since been published in Martínez *et al.*, *Oncogene*, 24:4106-4113, 2005 (of record) and Fang *et al.*, *Lymphatic Res. and Biology*, 7: 189-196, 2009 (provided herewith as **Exhibit D**)" (Declaration, ¶10).

Similarly, Figure 6 shows the effect of compound 77427 on GRP-stimulated angiogenesis in a directed *in vivo* angiogenesis assay (DIVAA). The DIVAA method and the interpretation of the results in Figure 6 are both described in Example 7 of the specification at page 36, lines 11-23. Dr. Cuttitta describes the DIVAA method and the results presented in Figure 6 as follows:

"In [this]the assay [described in Figure 6], silicone tubes with only one end open (angioreactors) were filled with 20 µl extracellular gel matrix (matrigel), either alone or mixed with GRP and/or a GRP inhibitor. After the matrigel solidified, the angioreactors were implanted into the dorsal flanks of athymic nude mice. After 11 days, the mice were injected intravenously with 25 mg/ml FITC-dextran 20 minutes before removing angioreactors. Quantitation of neovascularization in the angioreactors was determined as the amount of fluorescence trapped in the implants and was measured in a HP Spectrophotometer. Thus, greater relative fluorescence units (RFU) shown in Figure 6 indicates more angiogenesis, and less RFU indicates less angiogenesis. As shown in Figure 6, angiogenesis is stimulated in the presence of GRP. This stimulated angiogenesis is inhibited in a dose-dependent manner as the concentration of compound 77427 that is added with GRP is increased" (Declaration, ¶11).

In the Advisory Action, the Office maintains that compound 77427 is not unequivocally described in the specification as a GRP inhibitor because the various compounds described in the specification are generally identified as "modulating compounds." The Office notes that at page 11-12 of the specification, several GRP-affecting compounds are said to "modulate" the activity of GRP, including compound 77427. Applicants submit that at the passage indicated by the Office, the specification lists GRP antagonists (such as compound 77427) as well as GRP superagonists (such as a compound of formula XVII; *see* Table I, page 19). As Dr. Cuttitta states:

> "The specification indeed describes both agonists and antagonists of GRP, and these compounds are grouped together under the label 'modulating compounds.' However, when these compounds are described individually (for example as in Table 1 at pages 18-19 of the specification), the compounds are labeled according to their particular characteristics. Thus, compound 77427 is clearly labeled in Table I as an antagonist of GRP-stimulated second messenger activity. I note that such general and specific labels are commonly used in the art. *See* for example, Martinez *et al. Endocrinology*, 145:3858-3865, 2004 (of record). Similarly, in **Exhibit D**, agonist and antagonist compounds are referred to together as "regulators," but specifically designated as "agonists" or "antagonists" as appropriate when discussed individually" (Declaration, ¶13).

In light of the foregoing, Applicants submit that the specification provides ample evidence that compound 77427 can and does inhibit GRP function.

Compound 77427 can be used to treat GRP-associated conditions

In his Declaration, Dr. Cuttitta states: "Based on the data provided in the specification, I conclude that the ability of compound 77427 to inhibit GRP activity can be extended to treatment of various conditions where GRP activity has been implicated" (Declaration, ¶14). This conclusion is based in part on the data presented in Figure 6 of the specification that shows that compound 77427 functions like a well-known inhibitor of GRP, antibody 2A11. Dr. Cuttitta states in his Declaration:

> "Figure 6 also shows that the inhibitory effects of compound 77427 on GRP-stimulated angiogenesis are similar to the effects of the known GRP inhibitor, antibody 2A11. Both agents affect GRP-stimulated angiogenesis in a dose-dependent manner. As discussed below, antibody 2A11 has been used extensively in my laboratory and by others in experiments to inhibit proliferation of multiple cancer cell types and to treat chronic lung disease in an animal model. Thus, Figure 6 not only demonstrates that compound 77427 inhibits GRP function, but also illustrates that compound 77427 inhibits GRP function in the same way as a known GRP inhibitor that has been previously used to treat GRP-stimulated disease" (Declaration, ¶12).

In the Advisory Action, the Office questions whether it is possible to compare the effects of compound 77427 and antibody 2A11, as presented in the specification. As Dr. Cuttitta states in his Declaration:

"I understand that the Office questions this conclusion in part because "compound 77427 and compound 2A11 in Figure 6 are administered at significantly different amounts" (Advisory Action, page 3). Compound 77427 and monoclonal antibody 2A11 are different types of GRP-inhibitory molecules, and so one of ordinary skill would not be surprised if different units of concentration were used in their administration and different amounts are administered. In addition, the actual concentrations of compound and antibody used are in fact quite similar. The units of antibody administered in Figure 6 can readily be converted from µg/mL to nM, using 150 kDa (150,000 g/mol) as the recognized approximate molecular weight of an IgG (such as antibody 2A11). In Figure 6, the maximum effective concentration of compound 77427 is **500 nM**. The maximum effective concentration of antibody 2A11 is 100 µg/mL. When converted into nM, this concentration is approximately **670 nM** (100 µg/mL X 150,000 g/mol). Thus, Figure 6 demonstrates that compound 77427 and antibody 2A11 function at comparable maximum effective concentrations (500 nM versus 670 nM) (Declaration, ¶12).

Dr. Cuttitta further discusses the basis for therapeutic applications using compound 77427 as follows:

"As discussed above [in ¶12 of the Declaration], Figure 6 of the specification clearly demonstrates that compound 77427 inhibits GRP activity in an analogous manner to GRP neutralizing antibody 2A11. GRP neutralizing antibodies (*e.g.* antibody 2A11), which inhibit GRP activity by blocking GRP binding to its cellular receptor, are well known to the art (*see* for example, Cuttitta *et al., Nature*, 316:823-826, 1985; of record). These antibodies have been used to block GRP activity in many different contexts. For example, GRP neutralizing antibodies have been used to decrease proliferation of several types of cancer cells including lung cancer (*Id.*), pancreatic cancer (Avis *et al., Molecular Carcinogenesis,* 8:214-220, 1993; of record), and squamous cell carcinoma (Lango *et al., Journal of the National Cancer Institute,* 94:375-383, 2002; of record). Another exemplary use of GRP neutralizing antibodies has been to treat chronic lung disease in an animal model of brochopulmonary dysplasia (BPD) (Sunday *et al., The Journal of Clinical Investigation,* 102:584-594, 1998; of record). Because compound 77427 inhibits GRP activity in an analogous manner to GRP neutralizing antibody 2A11, I understand and could reasonably predict (through sound scientific reasoning) that compound 77427 will provide a therapeutic benefits similar to those previously observed with GRP neutralizing antibodies (such as antibody 2A11)" (Declaration, ¶14).

In light of the foregoing, Applicants' arguments of record, and the Declaration submitted herewith, Applicants submit that the description of compound 77427 in the specification enables one of skill in the art to practice the invention as claimed without undue experimentation.

Applicants respectfully request withdrawal of the enablement rejection of claims 80, 81, 90 and 92-97.

Request for Rejoinder of Withdrawn Claims

Applicants submit that based on the foregoing arguments, one of skill in the art would be able to practice the invention described by generic claim 90 without undue experimentation. As generic claim 90 is in condition for allowance, Applicants request that the species in withdrawn claim 91 be rejoined and examined at this time.

Request for Examiner Interview

The foregoing Amendment places this application in condition for allowance, and Applicants request that a Notice of Allowance be issued.

If any questions remain in view of this submission, the Examiner is formally requested to contact the undersigned in order to arrange a telephonic interview. It is believed that a discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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